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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/625,100	07/22/2003	Santiago Munne		8781

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/625,100	MUNNE, SANTIAGO	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/28/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/22/08 has been entered.

Applicants' Amendment to the claims, filed 10/15/08, is found to be compliant and has been entered. Claims 6 and 7 are amended, claims 5-8 are pending and under current examination.

Applicants did not file any substantive remarks with the amendment, filed 12/7/07, therefore, the Examiner responds to the remarks filed 10/15/08.

Claim Status

It is noted that claim 6 has been given the status identifier of "currently amended" however, upon careful examination, it appears that there is no current amendment to this claim, as the language is identical to that submitted in the claim set of 12/7/07. In the interest of compact prosecution, the Examiner presumes that the correct status identifier of this claim should read "previously presented". Applicants are advised to provide the correct status identifier to the claim upon response to this Office action.

Information Disclosure Statement

Applicants' IDS, filed 8/28/08, has been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-8 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained for reasons set forth in the prior Office action, mailed 3/5/08 and 3/23/07.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Applicants' Arguments & *Examiner's Response.* Applicants appear to discuss a scope of enablement as an argument (p. 1 of the Response). However, the Examiner notes that the Non-Final Office action (mailed 3/23/07, p. 3) and the Final Office action (mailed 3/5/08, p. 2-3) make clear that the invention has no enabled scope. Applicants' citation, with regard to hybridtech V. Monoclonal antibody, as well as *In Re Ruschig* is directed to Written Description. This rejection is not a Written Description rejection, but an Enablement rejection. Applicants' arguments with regard to Thomson not teaching that trisomic cell lines can revert to "normal" is directed to the rejection under §102, not under 112, 1st, enablement. The Examiner responds that Thomson is used with regard to how pluripotent cells are characterized. That is, Thomson provides guidance as to art-recognized properties of pluripotent stem cells.

Applicants argue that the Examiner brings in a new ground of rejection, which is the Wands factor (see pp. 1-2, bridging ¶). The Examiner notes that the Wands factors are not part of a new rejection. The rejection of enablement, for the claimed invention, has been maintained in prior Office actions. The Wands factors are the standard that is used to determine if an invention is enabled. See, MPEP §2164.01, Test of Enablement, which states, in part, that:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde,* 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? ***That standard is still the one to be applied. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).*** Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). See also *United States v. Telectronics, Inc.,* 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."). (Emphasis added)

Applicants argue that no undue experimentation exists for testing a stem cell for markers, such as Tra-1-60, SSEA-1, SSEA-3, SSEA-4, Tra 1-81, Oct-4 or alkaline phosphatase. Applicants argue that the epitopes for these antibodies are known and therefore, no undue experimentation would be required to determine if a population of cells expresses these markers. See p. 2, 1st ¶. Applicants argue that this did not require any undue experimentation because the methods to test if this epitope was expressed are known in the art and provide the Sadowy affidavit to support these methods. See p. 2, 2nd ¶ of the Response.

These arguments are not persuasive. The Examiner is not suggesting that testing cells to see if a particular epitope is expressed would be undue. The Examiner's arguments and the prior rejection are directed to the fact that

pluripotent stem cells have particular, art-recognized properties. Not only do these cells require expression of particular markers, but that they have specific phenotypes, and characteristics, such as specific differentiation ability. The specification only discusses karyotypic analysis of the resultant disomic cell lines. Applicants' have only shown that their cells have Tra-160. There is no indication of any other marker expression in Applicants' cells. Additionally, there is no other characterization of Applicants' cells, and Applicants have not provided sufficient guidance or teachings with regard to the resultant cells that are produced by their method, such that one of skill in the art would recognize that they had the art-accepted characteristics of embryonic stem cells. For example, Applicants have not shown that the cells are capable of differentiation into cells of the three germ layers, which indicates the differentiation potential of the cells.

The Sadowy declaration discusses analysis of trisomic embryos, the plating of blastocysts on human fibroblast feeder cells, and the passage of the resultant colonies and analysis of the resultant cells which showed that the specific cell line, after 1 month of culture continued to have 3/22 cells had trisomy 18, 0/22, trisomy 16 and 14/22 were disomic for all chromosomes tested. The Declaration further teaches Tra-1-60 binding to cells. The Declaration does not show that the cells that bind Tra-1-60 are disomic, there is no karyotypic analysis of the cells. Furthermore, the Declaration does not show any other characterization of the cells other than the potential expression of this particular marker, which the Examiner has shown can be expressed in other cell types. There is no indication that the cells are undifferentiated; merely that they express Tra-1-60. The Declaration is not persuasive.

Applicants provide the article of Lavon *et al.* to show enablement for the claimed invention. See pp. 2-3 bridging ¶ of the Response. These arguments are not persuasive. The Lavon article is not within the scope of the claimed invention because the Lavon article appears to use different techniques that that which is

instantly claimed. For example, the instant methods discuss culturing trisomic embryos on inactivated mouse feeder cells, maintaining the mouse feeder cells in maintenance medium comprising DMEM without sodium pyruvate, glucose 4500 mL-1, supplemented with 20% FBS, 0.1 mM mercaptoethanol, 1% non-essential amino acids

The methods taught by Lavon discuss hatching the blastocysts, culturing the blastocysts in G2V3 blastocyst medium, various steps of washing the blastocyst, removal of the ICM, and then culture of the ICM on mouse MEFs on a feeder layer supplemented with 30 ng/ml of bFGF until establishment of the colony.

Additionally Lavon teach different method steps than the claimed invention in that they teach 1) hatching the embryos in G2V3 medium, not culturing them on mouse feeder cells (as in step (a) of claim 7); 2) Lavon teach utilizing G2V3 medium, Applicants' invention does not appear to use this medium; 3) Applicants' medium contains 20% FBS, whereas Lavon does not appear to use serum in culturing of blastocysts/ICM; 4) Lavon uses 30 ng/ml of bFGF to establish the colonies for 5-12 days (p. 3, col. 1), whereas Applicants' invention utilizes 4 ng/ml of bFGF for 12 days; 5) Applicants' invention utilizes LIF (step c) of claim 7) whereas Lavon does not. Therefore, given that Lavon utilize different method steps, with different reagents, it is not possible to compare the methods taught by Lavon, with regard to the claimed invention. Additionally, any characteristics of the cells, taught by Lavon cannot be correlated to the cells taught by the instant invention.

Accordingly, it is maintained that:

1. The working examples do not provide sufficient guidance or teachings with regard to the characterization of the embryonic cells that are produced by the claimed method. In particular, the specification provides no guidance, other than the karyotypic analysis of the resultant disomic cells. There is no guidance with regard to if the cells are pluripotent, express appropriate markers, or have any of

the art-recognized characteristics of embryonic stem cells. As stated in the prior Office action,

2. The specification only provides a contemplated use with regard to embryonic **stem** cells. See, for example, page 3, paragraph 8 of the specification, which discusses the isolation of stem cells from the resultant diploid cells. There are no teachings or guidance provided by the specification with regard to the isolation of non-embryonic stem cells (i.*e.*, "embryonic cells", see claim 7, step (f)) from the diploid cell lines produced, or what these embryonic cells (which are not stem cells) would be used for.

In a final point, the Examiner notes that step e) of claim 7 recites that the cell lines are fixed and analyzed by FISH analysis. The claims require the production of disomic cell lines. A cell line requires that the cells be alive. The fixing and analysis by FISH of step e) would kill the cells. Therefore, this method step is not enabled.

The standard, under 112, 1st ¶, for enablement is that the specification must provide guidance on how to make and use the claimed invention. One of skill would not be able to make embryonic *stem* cells from the teachings of the specification, because there is no guidance with regard to the disomic cell lines that are produced from the trisomic embryos, in particular, that they have any of the art-recognized characteristics of embryonic stem cells. One of skill would not know how to make and use embryonic cells that are not stem cells that are encompassed by the claims, because the specification provides no guidance with regard to the isolation or characterization of these cells which are not stem cells, or what the cells would be used for.

Accordingly, in view of the state of the art of embryonic stem cells, namely the specific, art-recognized characteristics of such cells, the lack of teaching, guidance or characterization of cells produced by the claimed method, other than karytotypic analysis of the cells, the unpredictable state of the art of producing

embryonic stem cells, and the lack of guidance or teaching provided by the specification to overcome these unpredictibilities, the lack of teaching or guidance with regard to how to make embryonic cells that are not stem cells, it would have required undue experimentation for one of skill in the art to make and use the claimed disomic cell lines.

Claim Rejections - 35 USC § 112

The prior rejection of claims 7-8 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of Applicants' Amendment to the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Applicants provide the same remarks for both rejections of record; therefore, the Examiner addresses these arguments below:

Applicants' Arguments. Applicants argue that regarding the creation of uniparental stem cell lines, they are still in the process of demonstrating this point and that Thomson do not teach uniparental studies on their stem cells, Applicants argue that the claimed cells are unique.

Response to Arguments. These arguments have been considered, but are not persuasive. It is reiterated that Applicants are arguing limitations that are not found within the claims. There is no requirement with regard to the uniparental/biparental nature of the cells. There is no requirement that the cells

have one chromosome set from one parent. Applicants have not provided guidance to show that their cells have this characteristic because they are still running experiments to demonstrate this property. The as-filed disclosure discusses various ways in which a trisomic cell line can revert to disomic, such as anaphase lag, non-disjunction and chromosome demolition. Anaphase lag results in a disomic cell and a trisomic daughter cell. Non-disjunction results in a viable disomic cell and one lethal quadrisomic cell. Chromosome demolition results in deliberate fragmentation of one of the three chromosomes during metaphase or anaphase, resulting in two disomic daughters. See p. 5 of the Specification. There is no indication from any evidence of record that Applicants' claimed cells' chromosomes are uniparental. The claims do not distinguish Applicants' cells from those of the art. The Examiner maintains that the claims are product-by-process claims, wherein the specification provides no guidance to show differences between Applicant's cell lines and disomic cell lines taught by either Thomson or Shamblott. The requirement for the claims is that the cell lines are disomic, and this is fulfilled by the cited references.

Therefore the art of record is maintained.

Additionally, the Examiner notes that Lavon *et al.* (IDS) test homozygosity/heterozygosity in the cell lines that they make and state that there is clear heterozygosity in the analyzed chromosomes (p. 6, 1st col., 1st ¶). Similarly, Munne *et al.* (IDS) state that, "Regarding the aneuploidy correction hypothesis, Lavon *et al.* (2008) elegantly ruled out duplication of the monosomic chromosome by detecting heterozygosity7 at multiple loci of the affected chromsoome. This clear indicates the presence of two homologous chromosomes of different parental origin." See p. 2, 2nd ¶ of the Reference. Thus, even if Lavon enabled in the claimed invention (see Examiner's arguments with regard to this point, above), it is clear from both Lavon and Applicants' own statements that the chromosomes come from

a different parental origin, not a uniparental origin. The prior rejections of record are maintained for reasons set forth above and of record.

Claims 5 and 6 stand rejected, as applied to now cancelled claims 1-2, under 35 U.S.C. 102 (b) as being anticipated by Thomson [WO 96/22362, published 25 July 1996]. This rejection is maintained for reasons of record, advanced in the prior Office action, mailed 11/23/05 and 3/23/07.

Thomson teach the isolation and purification of primate embryonic stem cells that are capable of indefinite proliferation *in vitro* in an undifferentiated state, are capable of differentiation to derivatives of all three embryonic germ layers, and maintain a normal karyotype throughout prolonged culture. The pluripotent cells are negative for SSEA-1, positive for the SSEA-3 marker, positive for the SSEA-4 marker, TRA-1-60, TRA-1-81 and alkaline phosphatase. Thomson teach that the primate cells can continue to proliferate in an undifferentiated state for at least one year. See p. 7, lines 9-32. Thomson teach that tumors formed after injection of rhesus ES cells into the hindleg muscles of SCID mice [see Figure 5].

Accordingly, Thomson *et al.* anticipate the claimed invention because they teach a disomic cell line, and particularly, a disomic, embryonic stem cell line.

Claims 5 and 6 stand rejected, as applied to now cancelled claims 1-2, as being anticipated by Shamblott *et al.* [**PNAS**, 95:13726-13731 (1998)].

Shamblott teach that human pluripotent stem cells were isolated from gonadal ridges and mesenteries of 5- to 9-week postfertilization human embryos. Cells were cultured and subsequently passaged onto a mouse STO fibroblast feeder layer. Shamblott teach that embryoid bodies were collected from cultures and immediately embedded or replated into single wells [under conditions using mouse embryo fibroblasts, human fetal fibroblasts, or gelatin-coated tissue culture, see p. 13729, 1st column, 1st full ¶] and cultured for 14 days in the absence of hrLIF, hrbFGF and forskolin. See pp. 13726-13727, *Materials and Methods*. They teach

that immunohistochemical analysis of embryoid bodies demonstrated that the cells could differentiate into a variety of cell types, including derivatives of the three embryonic germ layers. See p. 13729, 2nd column, 1st full ¶. They teach that these cellsl are karyotypically normal (see Abstract, and Material and Methods).

As Shamblott *et al.* teach a disomic cell line, and in particular, an disomic, embryonic stem cell line, they anticipate the claimed invention.

Claims 5 and 6 stand rejected, as applied to now cancelled claims 1-2, as being anticipated by Thomson *et al.* (**PNAS**, 92:7844-7848 (August 1995)).

Thomson *et al.* teach pluripotent primate embryonic stem cells, isolated from a rhesus monkey blastocyst. They teach that these cells remain undifferentiated in culture in continuous passage, maintain a normal karyotype, express appropriate cell markers [alkaline phosphatase, SSEA-3, SSEA-4, TRA-160-, TRA-1-81] and, when injected into SCID mice, they consistently differentiate into derivatives of all three germ layers. See *Abstract* and p. 7845-7846.

Accordingly, as Thomson teach a disomic stem cell line, they anticipate the claimed invention.

Claims 5 and 6 stand rejected, as applied to now cancelled claims 1-2, as being anticipated by Thomson [**U.S. Pat. No.** 6,200,806 B1, March 13, 2001].

Thomson teach the preparation of a primate embryonic stem cell line that has expresses the cell surface markers characteristic of embryonic stem cells, have normal karyotypes, are able to proliferate in an undifferentiated state in continuous culture, and the ability to differentiate into all tissues derived from all three embryonic germ layers (see Abstract and claims).

Thus, because Thomson teach a karyotypically normal, disomic human embryonic stem cell line, they anticipate the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/
Primary Examiner, Art Unit 1632